MSAC Application 1774

Newborn bloodspot screening for glycogen storage disease, Type II (Pompe disease)

PICO Set 1

Population

Describe the population in which the proposed health technology is intended to be used:
Universal newborn bloodspot screening (NBS) for glycogen storage disease type II (GSD II; commonly known as Pompe disease) is proposed for all newborns who undergo testing via NBS programs in Australia. NBS uptake is currently estimated at 99.3% of Australian newborns (Huynh et al. 2022).

Natural history of the condition

GSD II is a type of lysosomal storage disorder (LSD) that leads to progressive neuromuscular deterioration and often death when untreated. GSD II is caused by an inherited deficiency of the lysosomal enzyme alpha-glucosidase which is required to break down glycogen. The accumulation of glycogen that results disrupts the cytoarchitecture and function of affected cells, leading to multisystem disease and often, early death.

GSD II is a single gene disorder that has an autosomal recessive inheritance pattern. Pathogenic variants of the alpha-glucosidase gene (GAA) cause reduced activity of the gene and hence a deficiency of the enzyme, and in some cases virtually no enzyme is produced. The most severe cases of GSD II are associated with very low or no GAA activity, whereas milder cases of GSD II occur when there is some degree of enzyme production.

As well as known common pathogenic GAA variants, non-pathogenic variants, variants of unknown significance (VUS), and pseudodeficiency variants are identified at genetic sequencing. A pseudodeficiency variant is one that causes a decrease in enzyme activity, but not sufficient to cause the disease. There are some known common pseudodeficiency variants, but these tend to be common to specific populations.

The two main categories of GSD II are infantile-onset and late-onset. All cases have the potential to be identified through universal NBS; however, screening will not always distinguish between the different categories of disease. Opinion varies on the age of onset amongst GSD II categories. In a US NBS program, the proportion of infantile-onset and late-onset cases identified from 274 positive screens confirmed by genetic diagnosis were 3.6% (10 cases) and 13% (36 cases) respectively. The proportion of pseudodeficiencies identified was 19% (53 cases) and cases with VUS was 2.9% (8 cases) (Klug et al. 2020). However, based on a large scale pooling of clinical studies in the US, about 28% of GSD II cases were found to be infantile-onset cases, of which approximately 85% were deemed classic infantile onset (Kemper et al. 2013).

Infantile-onset GSD II

The most severe form of GSD II is the classic infantile-onset form, where symptoms of cardiomyopathy occur at a median age of 3 months (Kishnani et al. 2010) along with other typical GSD II symptoms including respiratory failure and skeletal muscle weakness. Without treatment, most patients have unremitting deterioration, with death during the first year (median 6 - 8.7 months) from cardiac insufficiency (Kishnani et al. 2010).

The American College of Medical Genetics has classified infantile-onset into two forms: classic and non-classic. The classic infantile-onset form leads to severe cardiomegaly, hepatomegaly, hypotonia and early death. The non-classic form occurs more often after one year of age, but with a slower progression and less severe cardiomyopathy. The Australian study by Tchan et al reports that symptoms typically emerge at a median age of 2.6 years (range 6 months – 13 years)

(Tchan, M. et al. 2020b). Pooled clinical studies data suggest that about 85% of infantile-onset cases are the classic form (Kemper et al. 2013).

Late-onset GSD II

Late-onset GSD II is the other major subtype of GSD II. In a multinational survey of 255 children and adults (aged 2.6 to 81 years) with LOPD, the age at first presentation with a symptom ranged from 0 to 62 years and the age at diagnosis from 0 to 66 years. In a survey of 54 Dutch patients, the mean age of onset of symptoms was 28 years. 18 percent of patients had symptoms before 12 years of age (Hagemans et al. 2005a; Hagemans et al. 2005b). LOPD is characterised by a slower disease progression, compared to infantile-onset GSD II, primarily affecting skeletal muscles and often progressing to wheelchair confinement and eventual respiratory failure (Chin & Fuller 2022). Patients with late-onset GSD II do not develop cardiomyopathy but many subtypes are associated with significant morbidity and mortality due to neurological disorders. However, there is considerable variation in the age of symptom onset, and clinical presentation of late-onset GSD II can range from asymptomatic to severe. There is variability even in patients with identical variants, suggesting that secondary factors may influence the clinical course (Winkel et al. 2005).

In adolescents with late-onset alpha-glucosidase deficiency, the primary clinical finding is skeletal myopathy, eventually leading to respiratory failure (Engel 1970). Affected children usually present with delayed gross-motor development and progressive weakness in a limb-girdle distribution. Early involvement of the diaphragm is characteristic, often leading to respiratory failure and death in the second or third decade of life.

Affected adults with late-onset alpha-glucosidase deficiency also present with progressive, proximal weakness in a limb-girdle distribution, particularly the hip flexors in the earliest stages of the disease (Beltran Papsdorf, Howard & Chahin 2014). The weakness is accompanied by diaphragmatic involvement, leading to respiratory insufficiency early in the course of the disease.

Characteristics of an Australian GSD II population

Generally GSD II has an estimated incidence of about 1/47,000 in Australia (Chin & Fuller 2022), however it varies based on ethnicity. A recent global estimation of incidence was 1/23,000 (Park 2021).

A publication in 2020 described the clinical characteristics associated with an Australian GSD II population (Tchan, M. et al. 2020b). Despite significant overlap, they provide a guide to diagnosis in the subpopulations of GSD II.

For classic infantile-onset GSD II the residual alpha-glucosidase cut off for diagnosis was <3%, and symptom presentation began before 3 months of age. For non-classic infantile-onset GSD II residual alpha-glucosidase activity was expected to be 3-30%, with symptoms usually presenting between 6 and months and 13 years of age (median 2.6 years). Further details can be seen in Table 1 In the publication, juvenile-onset GSD II is a third category of GSD II, however it is usual to consider the juvenile-onset form a more severe category of late-onset GSD II (Tchan, M. et al. 2020b). For late-onset GSD II the residual alpha-glucosidase cut off for diagnosis was 3-30%, with symptom presentation between 29 and 33 years of age. Further details can be seen in Table 2.

Table 1 *Characteristic features and symptoms suggestive of Infantile-Onset GSD II*

Characteristic clinical features	Common presenting signs and symptoms
Sub-category: classic infantile-onset GSD II	
Residual GAA activity <3%	Cardiomyopathy/cardiac conduction disorders
Presentation <3 months from birth	Hypotonia/muscle weakness
Median age at diagnosis 4.7 months	Respiratory distress
Median survival (untreated)8.7 months	Repeated respiratory infections
	Feeding difficulties
	Failure to thrive
	Macroglossia
	Hepatomegaly
Sub-category: non-classic infantile-onset GSD II or juvenile-onset GSD II	
Residual GAA enzyme activity 3-30%	Delayed motor development
Symptoms typically emerge in childhood (median 2.6 years; range 6 months -13 years)	Symptoms related to limb-girdle muscle weakness: frequent falling, difficulty in climbing stairs, problems with running and sports
Diagnosis (median 4 years, range 0-16)	Difficulty raising the head in supine position
	Scoliosis
	Fatigue
	Asymptomatic, moderate elevation in creatinine kinase

Abbreviations: GAA = alpha-glucosidase; GSD II = glycogen storage disease II

Source: (Tchan, M. et al. 2020b)

Table 2 *Characteristic features and symptoms suggestive of Late-Onset GSD II*

Characteristic clinical features	Common presenting signs and symptoms
Residual GAA enzyme activity 3-30%	Myalgia and/or fatigue
Symptoms commonly present in adulthood (29-33 years)	Progressive muscle weakness (mainly axial and lower limbs)
Typically there is a delay of several years before a diagnosis is made	Symptoms related to limb-girdle muscle weakness: frequent falling, difficulty in climbing stairs
	Exercise intolerance and dyspnoea after moderate exercise
	Diffuse muscular pain, lumbar pain and muscle cramps
	Recurrent respiratory infections
	Morning headaches
	Nocturnal hypoventilation/hypoventilation
	Weight loss
	Difficulty with chewing/swallowing (bulbar weakness)
	Cardiac arrhythmias
	Hearing loss
	Asymmetrical ptosis
	Asymptomatic, moderate elevation in creatinine kinase
	Liver function abnormalities with raised AST and ALT for many years before muscle symptoms
	Urinary and bowel incontinence

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; GAA = alpha-glucosidase; GSD II = glycogen storage disease II

Source: (Tchan, M. et al. 2020b)

Genetics

GSD II is associated with allelic heterogeneity. The GAA gene is located in chromosome 17q25.2-q25.3 and so far more than 634 variants causing the disorder have been reported (Hahn 2021), and this number continues to expand each year as new variants are identified (Kishnani et al. 2019). Common variants have been described in a number of populations with a higher incidence (such as Israel, Taiwan, and the Maroon population of French Guiana), and include pseudodeficiency alleles (a variant that reduces GAA enzyme activity but does not cause disease, leading to false-positive diagnoses) (Chiang et al. 2012).

The estimated carrier frequency of GSD II based on genome aggregation database and currently available locus-specific databases was reported to be 1.3% in a global review (Park 2021).

Table 3 *Common GAA variants and associated phenotype or pathology*

GAA Variant	% of Affected Individuals	Phenotype / Pathology
p.Glu176ArgfsTer45	34% of Dutch population 9% of US population	results in negligible GAA enzyme activity and must be considered one of the more severe alterations, predicts IOPD
p.Gly828_Asn882del	25% of Dutch & Canadian infants 5% of US population	results in negligible GAA enzyme activity and must be considered one of the more severe alterations, predicts IOPD
c.-32-13T>G	36%-90% of persons w/late-onset GSD II	resulting in greatly diminished, but not absent, GAA enzyme activity, not associated with IOPD
p.Asp645Glu	≤80% of Taiwanese & Chinese infants	seen in a high proportion (≤80%) of IOPD in Taiwan and China
p.Arg854Ter	≤60% of persons of African descent w/a common phenotype	frequently associated with IOPD

Source: (Leslie N and Bailey 2007). Additional data available from de Faria et al, 2021.

Treatment

Treatment is available for this condition and funded through the life-saving drugs program (LSDP) when eligibility criteria are met. More detailed information on treatment is available in the intervention section of this PICO set.

Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed health technology, describing how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the technology:

Screening in the NBS program occurs in an unselected newborn population; there are no other eligibility criteria that apply.

Provide a rationale for the specifics of the eligible population:

The rationale for testing all newborns is to identify GSD II cases early so that appropriate treatment or monitoring can be initiated.

Infantile-onset GSD II

Findings from clinical studies suggest that early identification and treatment of classic infantile-onset GSD II can lead to decreased morbidity and mortality compared to diagnosis at the time of clinical presentation (Kemper et al. 2013). Considering the rapid progression of the disease, timely diagnosis and treatment are important; even slight delays can remarkably alter the course of the

disease (Hassnan et al. 2022). NBS can lead to an early diagnosis and enable access to presymptomatic enzyme replacement therapy (ERT) initiation. This has been shown to prevent cardiac and respiratory complications and helps in achieving normal growth and development in patients with infantile-onset GSD II (Hassnan et al. 2022). Kemper et al (2013) reported mortality rates at 12 and 24 months in screened and unscreened infantile-onset GSD II patients in their review, shown in Table 4 (Kemper et al. 2013).

Table 4 *12 and 24-month mortality for infantile-onset GSD II in screened and clinically diagnosed populations*

Population	**Detected through screening (%) (n=5)**		**Clinically detected (%) (n=9)**	
Age	Survival	Ventilator-free survival	Survival	Ventilator-free survival
12 months	100	100	100	100
24 months	100	100	89	67

Source: (Kemper et al. 2013). See Key Question 2 and Table 3.1 for full information

Late-onset GSD II

The diagnosis of the late-onset form is often difficult because it can clinically resemble a range of other neuromuscular disorders (Cupler et al. 2012). Hence a high level of clinical suspicion is needed for a timely diagnosis, if not known previously (Kishnani et al. 2006). Imaging and histologic studies suggest that there is muscle damage by the time that cases of late-onset GSD II are clinically detected (Kemper et al. 2013). Though ERT is not recommended for asymptomatic individuals, ERT is recommended at the earliest sign of clinical involvement in patients who are being monitored (Kishnani et al. 2006). This can only occur in individuals in whom it is known the condition is present, for example those identified through cascade testing.

A systematic review and meta-analysis published in 2022 concluded that ERT has a significant beneficial effect in the improvement of walking distance in late-onset GSD II patients and a non-significant improvement of muscle strength. No improvement in respiratory capacity was found in this study (Sarah et al. 2022).

A study from the Pompe Registry (Massachusetts, United States) of 396 patients demonstrated that respiratory function, as determined by FVC (forced vital capacity) was more impaired in patients with late-onset GAA deficiency who were older at ERT initiation or in those with a longer time from onset of symptoms or diagnosis to time of ERT initiation. Respiratory function remained stable while on ERT. Based on the findings, the authors concluded that the magnitude of benefit from earlier initiation of ERT was clinically meaningful (Stockton et al. 2020).

A published study that examined the newborn screening of GSD II for six years in Missouri (US) reported screening approximately 467,000 newborns for GAA activity. As a result of this screening, 46 newborns were diagnosed with GSD II, including 10 with infantile-onset GSD II (Klug et al. 2020). The study suggests that early initiation of ERT led to normal development and cardiac improvement for the majority of the infantile onset GSD II cases, and only one patient has discontinued ERT due to infusion-related reactions. Of the 23 later-onset cases that were still in active follow-up, 20 patients were stable and did not require ERT. One out of the other three cases required ERT, following worsening of condition that was picked up during monitoring.

Intervention

Name of the proposed health technology:
The proposed health technology is universal NBS for GSD II through Australia's NBS programs.

Newborn screening for GSD II is carried out using mass spectrometry (MS) on a dried bloodspot sample (DBS) collected onto filter paper in alignment with existing practice in the NBS programs. MS will be used to identify levels of alpha-glucosidase, an enzyme which is deficient or absent in GSD II. An additional test for GSD II can be conducted on the sample as it is collected currently, so there is no additional resourcing required for sample collection nor is there any additional risk to the baby associated with collection.

Screening and subsequent diagnosis of GSD II may provide eligibility for enzyme replacement therapy (ERT) through the Life Saving Drugs Program (LSDP) in Australia. The full eligibility requirements (including exclusion criteria) can be seen in the LSDP for Pompe Disease guidelines.

Describe the key components and clinical steps involved in delivering the proposed health technology:
The identification of individuals at risk of developing GSD II is to be based on:

- A screening test, carried out in NBS laboratories
- Clinical assessment and confirmatory diagnostic testing for newborns with abnormal screening results.

This will lead to intervention where appropriate, and/or ongoing monitoring and surveillance of at-risk individuals.

Currently, NBS is conducted by collecting blood samples from all newborns onto filter cards. In the laboratory the bloodspots are punched out and used in reagents required for the various screening tests. Testing for GSD II will utilise the same DBS samples and is expected to employ a two-tiered method in Australian newborn screening laboratories based on:

- Measurement of alpha-glucosidase enzyme activity in DBS samples (first-tier screening test)
- Measurement of Cre/Crn levels in DBS samples or targeted genetic screening (second-tier screening test)

Measurement of alpha-glucosidase enzyme activity in DBS samples (first-tier screening test)

The first tier of this testing protocol measures alpha-glucosidase enzyme activity in the dried blood spot (DBS) by mass spectrometry (MS). Low alpha-glucosidase enzyme activity is suggestive of GSD II. Screening for reduced blood alpha-glucosidase is often multiplexed with other LSDs (either via fluorometric, digital microfluidics, or tandem mass spectrometry-based technologies), given that treatment is also available for these disorders (Mechtler et al. 2012). A kit with the ability to screen for six LSDs including GSD II using MS is available commercially in Australia.

Enzyme analysis of blood samples is not specific enough to enable the differentiation between infantile-onset and late-onset GSD II. However, alpha-glucosidase activity levels >1% have generally not been noted in patients with classic infantile-onset GSD II, therefore levels <1% can support the diagnosis of infantile-onset GSD II (Kishnani et al. 2019). Occasionally in adults, skin fibroblast samples or other tissue samples will be collected to do further testing, as they can give a more accurate concentration of alpha-glucosidase activity.

The assay in DBS samples is complicated by interference from non-lysosomal maltase glucoamylase, and therefore requires the use of inhibitors such as acarbose and assays at neutral and acidic pH to derive the required test sensitivity and specificity (Davison 2020).

State and territory screening laboratories will be consulted to determine their preferred approach for screening, to inform the health technology assessment for MSAC consideration during the PICO development stage. The use of a commercially available kit from Revvity or developing in-house methods was considered previously. If a collaborative national approach to procure the kit is used, it is estimated to cost approximately [redacted][1]. Some of the reactions however will be required for quality control samples, therefore will not equate to screening for [redacted] babies. The incremental cost of screening per child would be [redacted]. The kit is capable of detecting five other lysosomal storage disorders simultaneously (Gaucher Disease, Niemann-Pick A/B Disease, MPS I, Krabbe Disease and Fabry Disease), which would presumably improve the cost-effectiveness of an assessment of NBS for multiple conditions but does not alter the assessment of NBS for GSD II alone.

Abnormal results from first tier screening will result in repeat testing to confirm before progressing to second tier testing. Repeat testing with a higher cutoff value is currently used by the Taiwanese screening program which increases the positive predictive value of tandem MS enzyme activity screening from 0.5% to 9% (Chien, Hwu, & Lee, 2019).

Measurement of Cre/Crn levels in dried bloodspot samples or targeted genetic screening (second-tier screening test)

There are multiple methods which can be used for the second tier test for GSD II. Second tier methods can be used in addition to or in place of repeat first tier testing. The second tier test used must be adapted for use in Australian newborn screening laboratories. State and territory screening laboratories will be consulted to determine their preferred approach for screening, to inform the health technology assessment for MSAC consideration during the PICO development stage. Possible second tier methods include the biochemical quantification of creatine/creatinine (Cre/Crn) in DBS samples using tandem MS or targeted genetic screening of the *GAA* gene. *GAA* gene sequencing is required in the clinical assessment of GSD II to identify the pathogenic variant and the cross-reactive immunological material (CRIM) status of a patient. Including genetic sequencing within the screening program may enable more timely diagnosis to support early intervention.

[1] Source: expert advice

Repeat first-tier testing may be used in place of a second tier test in combination with the clinical assessment and diagnostic testing described below.

Clinical assessment and diagnostic testing

Both HEX4 and *GAA* sequencing can be used as confirmatory test for GSD II. To access treatment through the Life Saving Drugs Program (LSDP), DBS screening of alpha-glucosidase activity, and either a positive HEX4 assay or identification of a pathogenic or likely pathogenic variant (PV or LPV) by *GAA* sequencing is required for infantile-onset GSD II. Additional criteria are required for late-onset GDS II.

Due to the urgency in which treatment must be started when classic infantile-onset GSD II is suspected, an abnormal screen will be immediately clinically investigated. A urine HEX4 test will be requested concurrently with a repeat DBS for GAA activity or second-tier testing. Signs of cardiomyopathy will be investigated to identify classic infantile-onset GSD II (chest X-ray, echocardiogram or electrocardiogram). The presence or suspicion of cardiomyopathy following a positive screening result requires urgent management to get confirmatory testing and ERT initiated as soon as possible.

Urine HEX4 testing is usually chosen as a confirmatory test as it has a short turn-around-time compared to *GAA* sequencing, which, in the current setting, can take 6 weeks or more (expert advice). Glucotetrasaccharide (Glc4) is a metabolite of glycogen and is raised in people with GSD II. Excess Glc4 is excreted in the urine and can be used to screen and monitor GSD II in the HEX4 test. However, Glc4 can also be elevated in other glycogen disorders, so should be used in conjunction with other tests if other GSD disorders are suspected.

In those who are diagnosed with GSD II following a HEX4 assay, *GAA* sequencing will be performed to identify the pathogenic variant. The rate of detection of pathogenic, variants of unknown significance, and pseudodeficiency variants in Australia will depend on the prevalence of specific variants in this country. An estimate of the proportion of variants detected in a Missouri NBS program are given in the Intervention section of this document.

GAA gene sequencing is performed as the confirmatory test when the result is less urgent i.e. when there are no cardiomyopathy signs and late-onset GSD II is suspected. PCR-based sequencing of entire coding region, intron/exon boundaries, as well as known pathogenic variants (HGMD 2017.3) in the promoter and deep intronic regions of the specified gene is undertaken as part of the full gene sequence analysis (Cincinnati Children's).

GAA full gene sequence analysis is also used to characterise the case specific variants. Sequencing has the potential to distinguish between infantile-onset and late-onset forms, and also distinguish pseudodeficiency of alpha-glucosidase from genuine GSD II or variant of unknown significance (VUS) as there are some variants with known associations (Dasouki et al. 2014; Mechtler et al. 2012; Sawada, Kido & Nakamura 2020). However, there are now more than 634 recorded variants in *GAA* and sequencing is therefore limited in its ability to differentiate. An additional complication is that there is a large degree of variation in symptom severity across infantile-onset and late-onset cases. This is why clinical assessment is vital to diagnosis. For the purposes of screening, detection of a pseudodeficiency variant (i.e. a variant that lowers the enzyme level but not sufficiently to cause GSD II) is a false positive result. As an example of the

breakdown of the cases identified in an NBS program (Missouri, US) from 27,724 DBS screened for GSD II the following was confirmed:

- Two carriers of GSD II
- Three false positives (GAA activity normal, carriers status unknown)
- One case of pseudodeficiency,
- One case with likely classic infantile-onset GSD II
- One case of non-classic infantile-onset GSD II, and
- One case of late-onset GSD II.

Diagnostic criteria for GSD II disease by newborn screening

Diagnostic criteria have been established for NBS in other countries and jurisdictions. The US state of Missouri commenced newborn screening for GSD II in 2013. The predicted onset - infantile or late – was made at the time of confirmatory testing using biochemical test results, imaging, clinical presentation including presence of cardiomyopathy, and variant analysis. Table 5 below provides the criteria used to determine disease status in the Missouri NBS program. The final disease classification is made based on evaluation of all clinical information. Once confirmed, ERT is commenced as soon as possible for infantile-onset GSD II. For late-onset GSD II patients, treatment with ERT is typically delayed until the onset of symptoms or laboratory results consistent with progression of disease are observed (Klug et al. 2020).

Table 5 *Missouri Newborn Screening Criteria for Pompe disease*

Newborn Assessment	Classical Infantile	NonClassical Infantile	Later Onset	Genotype of Unknown Significance	Pseudodeficiency	Carrier
GAA enzyme activity	Absent or within affected range	Within affected range	Decreased	Decreased	Decreased	Decreased or normal
HEX4	Elevated	Elevated or WNL	WNL	WNL	WNL	WNL
Creatine Kinase (& other labs as indicated)	Elevated	Elevated or WNL	WNL	WNL	WNL	WNL
Chest x-ray, EKG, Echo	Abnormal	Mild abnormalities or WNL	WNL	WNL	WNL	WNL
Variant analysis	-Two pathogenic variants -One pathogenic variant and one or more VUS -Two VUS	-Two pathogenic variants -One pathogenic variant and one or more VUS -Two VUS	Two pathogenic variants -One pathogenic variant and one or more VUS -Two VUS	-One infantile variant and one or more VUS -One late onset variant and one more VUS -Two or more VUS	-Two psuedodeciency alleles	-One pathogenic variant -May or may not be in combination with pseudo alleles
Clinical presentation	Muscle weakness, poor muscle tone, feeding issues, cardio-mypoathy present	Muscle weakness or WNL	WNL at birth	WNL at birth	WNL at birth	WNL at birth

Abbreviations: HEX4 = Biochemical test for urinary glucotetrasaccharide; Echo = echocardiogram; EKG = elektrokardiographie; WNL = within normal limits; VUS = variant of unknown significance

Source: Klug et al 2020

An estimate of case numbers which will be detected by screening in Australia, based on a projection provided by Kemper et al (2013) in a US population[2] is given in Table 6. The data is also based on an estimated incidence of 2.14 cases per 100,000 of GSD II taken from Chin and Fuller (2022), and an annual birth estimate of 312,380 for the 2025-2026 financial year. The positive predictive value of screening will be highly dependent on the screening methods employed by the laboratories, including the choice of second tier test or the use of repeat screening.

Table 6 *Estimated cases detected through NBS for GSD II in Australia for the financial year 2025-2026*[2]

Screening results in 312,380 newborns	Rate	Number
Total positive screens	0.00655%	20
True positives	51.1% of positives	10
False positives	48.9%	10
Total negative screens	99.99%	312,360
True negatives	99.99%	312,359
False negatives	0.00025%	1

Treatment and ongoing management involved is covered under the next question due to the overlap between the two sections.

Identify how the proposed technology achieves the intended patient outcomes:

Infantile-onset GSD II

NBS for GSD II allows for early detection of the condition. In infantile-onset GSD II, favourable outcomes are strongly associated with very early initiation of intravenous ERT with recombinant human *GAA* (*rhGAA*). ERT has a positive impact on mortality and significantly lengthens survival. ERT also improves motor development and cardiac function in affected individuals. However, it is important to note that ERT should be initiated as soon as possible after a diagnosis for an optimal outcome. Delayed ERT by even few days can influence outcomes (Chien, Hwu & Lee 2013). NBS offers an early diagnosis and presymptomatic ERT initiation. It prevents cardiac and respiratory complications and helps in achieving normal growth and development in patients with IOPD (Hassnan et al. 2022).

A published study that examined the newborn screening of Pompe disease for six years in Missouri (US) reported screening approximately 467,000 newborns for GAA activity; as a result of this screening, 46 newborns were diagnosed with Pompe disease, including 10 with infantile onset Pompe disease (Klug et al. 2020). The study suggested that early initiation of ERT led to normal development and cardiac improvement for the majority of the infantile onset Pompe disease cases, and only one patient discontinued ERT due to infusion-related reactions. Of the 23 later-onset cases that were still in active follow-up, 20 patients were unchanged and did not receive ERT. Of the three remaining cases, cardiac symptoms improved without ERT in one,

[2] US projected data is reported in Kemper et al (2013), (Table C.6). The US data was calculated using screening rates identified in the Taiwan NBS program for GSD II which uses a fluorometric assay for DBS GAA. The data may not apply in an Australian setting.

cardiac and myopathy symptoms improved without ERT in the second, and in the third case hypotonia worsened and ERT was instigated at 13 years of age.
A health and economic microsimulation analysis done in the US concluded that newborn screening for GSD II resulted in substantial health gains for individuals with infantile-onset GSD II (Richardson et al. 2021). Infants with screened and treated infantile-onset GSD II experienced an average lifetime increase of 11.66 QALYs compared with clinical detection. The ICER was $379,000/QALY from a societal perspective and $408,000/QALY from the health-care perspective (Richardson et al. 2021).

Another benefit of diagnosis in newborns is ending the diagnostic odyssey, which can be extended due to the non-specific nature of symptoms, although this is likely to be the case for non-classic infantile-onset GSD II. Those with cardiomyopathy in the first three months do not have an extended diagnostic odyssey (expert advice).

Impact of CRIM status on ERT response

CRIM status is determined by a blood-based CRIM assay (Wang, Okamoto & Keutzer 2014). Patients with infantile-onset GSD II exhibiting residual AαGlu enzyme activity are CRIM-positive, and patients with infantile-onset GSD II exhibiting no residual AαGlu enzyme activity are CRIM-negative (Sawada, Kido & Nakamura 2020). Those who are CRIM-negative are at greater risk of developing antibodies to ERT which can neutralise the treatment (Kemper et al. 2013). One quarter of infantile-onset GSD II cases are CRIM-negative. Therefore, patients should undergo evaluation of CRIM status before receiving ERT. An optimal treatment response to ERT is reported in CRIM-positive patients. CRIM-negative patients develop neutralizing antibodies (immune response) for recombinant human lysosomal α-glucosidase (rhGAA) when receiving ERT, which impairs the effects of ERT. This leads to a worse prognosis compared to their CRIM-positive counterparts (Kishnani et al. 2010). Three quarters of infantile-onset GSD II cases are CRIM-positive. Prophylactic immune tolerance induction (ITI) with rituximab, methotrexate and intravenous immunoglobulin appears to minimise the immune response to ERT (Li et al. 2021).

Late-onset GSD II

The benefits of ERT in cases of late-onset GSD II are less clear than infantile-onset. The diagnosis of the late-onset form is often difficult because it can clinically resemble a range of other neuromuscular disorders (Cupler et al. 2012). Hence a high level of clinical suspicion is needed for a timely diagnosis, if not known previously (Kishnani et al. 2006). Imaging and histologic studies suggest that there is muscle damage by the time that the cases of late-onset GSD II are clinically detected (Kemper et al. 2013). Though ERT is not recommended for asymptomatic individuals, ERT is recommended immediately or at the earliest sign of clinical involvement upon monitoring (Kishnani et al. 2006). This requires prior knowledge of whether the individual is affected by this condition.

A systematic review and meta-analysis published in 2022 concluded that ERT has a significant beneficial efficacy in the improvement of walking distance in late-onset GSD II patients and a non-significant improvement of muscle strength. No improvement in respiratory capacity was found in this study (Sarah et al. 2022).

A study from the Pompe Registry of 396 patients demonstrated that respiratory function as determined by forced vital capacity (FVC) was more impaired in patients with late-onset alpha-

glucosidase deficiency who were older at ERT initiation or in those with a longer time from onset of symptoms or diagnosis to time of ERT initiation. Respiratory function remained stable while on ERT. Based on the findings, the authors concluded that the magnitude of benefit from earlier initiation of ERT was clinically meaningful (Stockton et al. 2020).

In late-onset GSD II treatment is usually only initiated when symptoms appear, but ERT has been associated with better outcomes when initiated before irreversible muscle damage in at least one study (Gragnaniello et al. 2022). This could potentially be achieved with NBS, as individuals identified with late-onset GSD II can be monitored for related signs and symptoms, and treatment initiated at the appropriate time. If late-onset GSD II is identified by NBS, monitoring would potentially be long-term and costly prior to onset of symptoms. In countries with a higher incidence of GSD II, there are existing treatment algorithms to follow-up asymptomatic late-onset GSD II patients every 3 months during the first year, and every 6–12 months thereafter. This includes evaluating biomarkers (CPK, AST, ALT, Glc4), conducting cardiac assessments (especially for rhythm disturbances), and assessing pulmonary and feeding status and psychomotor development; with age-appropriate scales (Gragnaniello et al. 2022).

Late-onset GSD II patients are not impacted by CRIM status, as they produce alpha-glucosidase to some degree. Those who are diagnosed early with late-onset GSD II (or their parents) can benefit from not having to go through an extended period of diagnostic odyssey. Not having a diagnosis can be associated with ongoing anxiety.

Eligibility for treatment in Australia

In Australia, current TGA-approved treatments include ERTs with a recombinant human acid α-glucosidase (rhGAA) to provide an exogenous supply of enzyme to treat the enzyme deficiency; with alglucosidase alfa and avalglucosidase alfa enzymes as the active ingredients.

These treatments are Myozyme (AUST R 136005, approved in March 2008) and Nexviazyme (AUST R 346495, approved in Nov 2021), which are indicated for the long-term treatment of patients with a confirmed diagnosis of GSD II, and can be administered for both infantile-onset GSD II and late-onset GSD II (TGA 2008, 2021). However, Nexviazyme can only be administered in patients aged one year and older. Potential side-effects include immunogenicity-related complications such as developing reactions to infusions and/or immunomodulation.

Both approved treatments are available under set criteria via the LSDP. Guidelines for the treatment of GSD II through LSDP, including the eligibility criteria for initial and ongoing treatment, are available on the Department website (Department of Health and Aged Care 2019).

Initial eligibility requirements for LSDP:

Patient aged up to 24 months:

- Documented diagnosis of infantile-onset GSD II

Patient aged over 24 months:

- Documented diagnosis of late-onset disease

Patient aged over 18 years:

- Documented diagnosis of late-onset GSD II,

AND at least one of the following criteria:

- Respiratory function test: Patients with Forced Vital Capacity (FVC), either supine or erect, less than 80% of predicted value. Both supine and erect FVC should be performed.
- Sleep disordered breathing: Patients with an apnoea/hypopnoea incidence of >5 events/hour of total sleep time or more than two severe episodes of desaturation (oxygen saturation <80%) in an overnight sleep study.
- Significant muscular weakness: Patients with significant muscular weakness as evidenced by Manual Muscle Testing (MMT) (employing the MRC score) of 4 or less in either limb girdle accompanied by a 6 Minute Walk Test (6MWT).

A treatment approved by the European medicines agency for GSD II is Pombiliti (cipaglucosidase alfa). It is a long-term ERT used in combination with the enzyme stabilizer miglustat for the treatment of adults with late-onset GSD II. This is, however, not currently available for use in Australia.

Potential harms of ERT

There are potential harms associated with ERT. It is now known that babies who are CRIM negative form antibodies against replacement enzyme, a reaction which can be lethal. To avoid this immunomodulation is given with ERT to CRIM negative infantile-onset GSD II patients. Because of the long turn-around-time in getting CRIM status results back from the laboratory, immunomodulants are given to all infants starting ERT in current clinical practice (according to expert clinical advice). By doing so, the delay in administering ERT can be minimized. Any harms from ERT (side effects, adverse events) need to be weighed against its benefits.

Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components?

☐ Yes
☒ No

Explain whether it is essential to have this trademark component or whether there would be other components that would be suitable:
N/A

Are there any proposed limitations on the provision of the proposed health technology delivered to the patient (For example: accessibility, dosage, quantity, duration or frequency):

☒ Yes
☐ No

Provide details and explain:
All families are offered NBS for their newborns. Screening is dependent on parental consent.

To implement screening, the adopted testing protocol would need to be implemented by the Australian NBS laboratories. Further, the screening protocol will need to be accredited by NATA

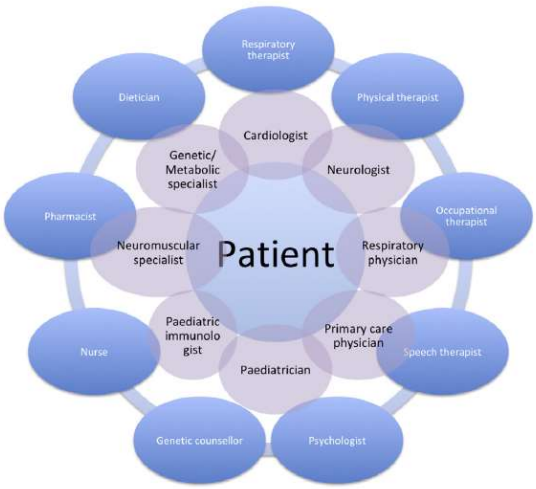
prior to implementation. Associated training will also be required for laboratory staff. Funding for screening will also need to be sought by NBS laboratories from their respective state budget cycles to procure necessary equipment and reagents.

If there is a significant increase in the number of patients diagnosed with GSD II (and other LSDs) that require surveillance, including mild cases or people with variants of unknown significance, further resourcing would be needed for providing adequate clinical care for these patients. For example, expert advice indicated that limited or no LSD specialists in Western Australia, Tasmania or Northern Territory, meaning these states rely on resources from other jurisdictions with sufficient expertise. Additional resources for follow-up annual testing, such as cardiac evaluations, to meet LSDP eligibility guidelines may also be required to remain within the required timeframe.

If applicable, advise which health professionals will be needed to provide the proposed health technology:
Screening for GSD II via NBS would occur through the existing NBS programs across Australia. Samples are collected under the same conditions and in the same settings, and does not represent an additional burden on sample collection. Laboratories may require extra staff to accommodate testing.

The health professionals required may vary from jurisdiction to jurisdiction, however, below is a potential list of key health professionals who may be needed:

1) Nurses/midwives who collect blood samples on NBS dried bloodspot cards. This process already occurs routinely to screen for other conditions, therefore, there is no additional workload at this stage.
2) Screening laboratory scientist/pathologist – these professionals are needed to undertake the screening, and will be required to develop and implement a screening and data analysis protocol for GSD II.
3) Clinical nurse consultants/ screening laboratory support staff will need to assist with recalls, parent notification or early notification of clinicians where there are abnormal results – limited change expected as this process already occurs for other conditions. They will also be required to provide referrals into care.
4) Genetic counsellor will be required for consultation and communicated test results.
5) If abnormal, follow up diagnostic testing will be required through the relevant children's hospital, an appropriate physician for diagnosis or through a genetic counsellor. If an external diagnostic screening lab was to be involved, there would likely not be a change due to the proposed health technology as diagnostic testing already occurs for GSD II.
6) Specialist metabolic physician required for consultation of positive cases.
7) If GSD II is confirmed, a multi-disciplinary team will be needed as this condition affects multiple body systems. A proposed multi- disciplinary team from consensus recommendation published for Australia in 2020 is provided below (Tchan, Michel et al. 2020a). The tertiary and quaternary hospitals in Australia are equipped with the adequate resources for a multidisciplinary management for GSD II. However expert advice suggests that an increase in babies identified with late-onset GSD II through NBS who require ongoing monitoring would require extra resourcing to the multi-disciplinary teams.



If applicable, advise whether delivery of the proposed health technology can be delegated to another health professional:
Not applicable

If applicable, advise if there are any limitations on which health professionals might provide a referral for the proposed health technology:
Not applicable

Is there specific training or qualifications required to provide or deliver the proposed service, and/or any accreditation requirements to support delivery of the health technology?

☒ Yes
☐ No

Provide details and explain:
As noted above, expert advice indicates a second-tier testing protocol will need to be adapted for use in Australian NBS laboratories. This screening protocol will need to be accredited by NATA prior to implementation. Associated training will also be required for laboratory staff.

Indicate the proposed setting(s) in which the proposed health technology will be delivered:

☒ Consulting rooms
☐ Day surgery centre
☐ Emergency Department
☒ Inpatient private hospital
☒ Inpatient public hospital
☒ Laboratory
☒ Outpatient clinic
☒ Patient's home
☐ Point of care testing
☐ Residential aged care facility
☐ Other (please specify)

Blood samples can be taken in many clinical settings and at home by qualified staff. Analysis of the samples will be undertaken by NBS laboratories.

Is the proposed health technology intended to be entirely rendered inside Australia?

☒ Yes
☐ No

Please provide additional details on the proposed health technology to be rendered outside of Australia:
N/A

Comparator

Nominate the appropriate comparator(s) for the proposed medical service (i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service:

Please provide a name for your comparator:
The comparator for the proposed health technology is no universal screening for GSD II (testing for GSD II that occurs at symptom presentation).

Please provide an identifying number for your comparator (if applicable):
Not applicable

Please provide a rationale for why this is a comparator:
Currently, in the absence of universal NBS, babies and adults are tested for GSD II when relevant symptoms are present or following the diagnosis of a direct family member (e.g., a parent or sibling). Intervention can only commence following the onset of symptoms and diagnosis.

Alternative comparator – targeted testing

In current practice targeted screening is offered to families with a known family history of GSD II, or of particular ancestry where GSD II is more prevalent. Targeted screening is offered in a setting where couples are considering pregnancy or are already pregnant. For couples were there has been identification of pathogenic GSD II variants in both parents, prenatal testing of the fetus can be offered. In couples who are not yet pregnant, preimplantation genetic diagnosis can be offered.

There is a paucity of data on previous comparative analysis seeking to determine whether universal NBS is the most appropriate approach compared to targeted screening or alternative methods. Targeted screening is generally difficult to use as a comparator because of lack of information about the effectiveness and costs of targeted versus universal screening (Prosser et al. 2012).

Diagnosis of infantile-onset GSD II at symptom presentation

Babies with infantile-onset GSD II present with cardiomyopathy, pulmonary, or neurological symptoms before 1 year of age. (Table 3 provides further criteria of infantile-onset GSD II). A clinical expert will order investigations into the symptoms, such as chest x-ray, dried bloodspot screening for alpha-glucosidase concentration, followed by urine tetrasaccharides assay, and blood alpha-glucosidase investigation. *GAA* sequencing will be ordered if indicated.

If there is low enzyme activity and cardiomyopathy is present, COIPD is diagnosed, prior to sequencing results being complete. Prior to starting ERT, CRIM status is determined. In CRIM-positive babies, ERT is started, and the addition of immunomodulation is considered for those at high-risk of antibody reactions to the therapy. In CRIM-negative babies, ERT is begun along with immunomodulation. Follow-up programs are begun, to review tolerance of ERT, and evaluate the progression of disease. Treatments are adjusted when required.

For cases where there is low enzyme activity but normal cardiac function, diagnosis of non-classic infantile-onset GSD II will depend on the *GAA* sequencing result, including analysis with parental DNA. Evaluation of symptoms such as muscle weakness, impaired pulmonary function, and subtle developmental delay occurs regularly. Sequencing results can provide input on whether pathogenic variants (PV), pseudodeficiency variants, a variant of unknown significance (VUS), or combination of variant types is present. If one or more pathogenic variants are present, the patient will continue to be monitored for symptom development, and ERT will be given at the initial signs. ERT will be administered with or without immunomodulation in cases of classic infantile-onset GSD II, depending on CRIM status.

If a PV is present in combination with a PUS or pseudodeficiency variant, monitoring will occur and if symptoms develop with enzyme status remaining low, a positive diagnosis of non-classic infantile-onset GSD II can be given and ERT offered. If two pseudodeficiency variants are present, the individual will be considered negative for GSD II. If symptoms continue to develop, another cause may need to be considered.

In this comparator scenario, babies will not be tested for infantile-onset GSD II until symptoms present, and therefore they will start ERT later than would be the case if diagnosis was made at birth. There is likely to be increased morbidity and mortality associated with later identification, as the condition is untreated for longer.

Diagnosis of late-onset GSD II at symptom presentation

For individuals with late-onset symptoms, a similar pathway will be followed as for non-classic infantile-onset GSD II except that there is often a delay of several years between symptom onset and diagnosis because of the non-specific nature of the symptoms. Table 3 provides further criteria of late-onset GSD II. For those with symptoms suggestive of GSD II, *GAA* sequencing will be ordered, and following the identification of a pathogenic GSD II variant, ERT may be administered if clinically indicated. However, individuals with confirmed diagnoses of late-onset GSD II cannot commence treatment before the age of 24 months, according to the LSDP guidelines for GSD II. Also, one of the TGA approved treatments (Nexviazyme) is not approved for patients under 1 year of age. As with infantile-onset GSD II, individuals with late-onset GSD II may have earlier and more severe symptoms due to receiving late rather than early diagnosis after NBS, and delayed ERT.

Pattern of substitution – Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator?

☐ None – used with the comparator
☐ Displaced – comparator will likely be used following the proposed technology in some patients
☐ Partial – in some cases, the proposed technology will replace the use of the comparator, but not all
☒ Full – subjects who receive the proposed intervention will not receive the comparator

Please outline and explain the extent to which the current comparator is expected to be substituted:

Conditions should be detected prior to symptom onset when screening is available, therefore it is expected that the comparator will be fully substituted by the health technology. If the uptake of NBS is taken into account, the rate of screening is expected to change from 0% (no NBS) to 99.3% (NBS for GSD II).

Outcomes

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

☒ Health benefits
☒ Health harms
☒ Resources

Health benefits

- Health outcomes from early diagnosis and intervention (survival, ventilator free survival, vital capacity, forced vital capacity, gross motor function measures)
- Quality of life (both the disease and the treatment may impact on quality aspects)
- Disease specific patient reported outcomes (PROs)

Health harms

- Impact of false positive results
- Impact of false negative results (noting this would mean the newborn is diagnosed clinically, which is the comparator. There is a potential that a diagnosis of GSD II may be overlooked if it is assumed it will be detected through NBS)
- Impact of diagnosing cases that are late-onset or have mild symptoms, pseudodeficiency cases, or variants of unknown significance
- Safety of ERT, prior to or after symptom onset, short and long-term effects.

Resources

- Financial impact of screening
- Financial impact of diagnosis, relative to existing practice (including false positives)
- Financial impact (including savings) of early intervention, relative to existing practice
- Financial impact of any change in clinical management following NBS (e.g., change in treatment approach when treatment occurs pre-symptomatically, genetic counselling, and other support services)
- Financial impact of ongoing monitoring and surveillance
- Cost effectiveness (cost per diagnosis; cost per QALY)

Other relevant considerations

- Value of knowing (family planning, emotional benefits/harms to family, social benefits/harms to family, noting these are secondary to the outcomes delivered to the baby)
- Accuracy of the screening test (sensitivity, specificity, positive predictive value and diagnostic yield).
- Ethical considerations (equity of access, considerations regarding consent, considerations regarding cascade testing, including notification of carrier status)

Outcome description – please include information about whether a change in patient management, or prognosis, occurs as a result of the test information:
In summary, there is expected to be a change in patient management if diagnosis of GSD II occurs following NBS. The expected change in management will be earlier initiation of treatment in babies with infantile-onset GSD II. The treatment is known to greatly improve morbidity and mortality, and if initiated before symptoms are present, can prevent irreversible damage to the body. For patients with early diagnosis of late-onset GSD II, knowledge of the condition facilitates monitoring that enables commencement of treatment as soon as clinically indicated, rather than waiting for symptoms and potentially spending years awaiting a diagnosis.

Change in management pathway

If universal NBS screening identifies a child with GSD II, diagnostic/confirmatory testing will be needed. Once confirmed, in infantile-onset GSD II, treatment should be initiated as soon as possible for an optimal outcome (Chien et al. 2009). Without treatment, most infantile-onset GSD II patients have unremitting deterioration, with death during the first one-to-two years of age from cardiac insufficiency (Winkel et al. 2005).

The baby's family should be referred to genetic counselling as soon as the diagnosis is confirmed. Cascade testing will allow reproductive planning and may also identify late-onset GSD II in people without symptoms.

In late-onset GSD II, while treatment is only initiated when abnormalities appear, ERT is associated with better outcomes when initiated before irreversible muscle damage.

The predicted onset—infantile or late—is made at the time of confirmatory testing using biochemical test results, imaging, clinical presentation including presence of cardiomyopathy, and variant analysis. The final disease classification is made based on evaluation of all clinical information.

For late-onset GSD II patients, treatment with ERT is typically delayed until the onset of symptoms or laboratory results consistent with progression of disease are observed (Klug et al. 2020). Early referral to a specialist is essential to formalise the surveillance protocol and to alert the family to signs of GSD II. Treatment should be started as soon as abnormalities are identified (Winkel et al. 2005).

Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)?

☒ Superior
☐ Non-inferior
☐ Inferior

Please state what the overall claim is, and provide a rationale:

The overall claim is that universal NBS for GSD II has superior safety and effectiveness compared to current practice (no universal screening) for diagnosis of GSD II.

There are significant clinical benefits for early diagnosis and early commencement of treatment. Commencement of treatment prior to symptom development delays the onset and reduces the severity of symptoms. This can be life saving for babies with infantile-onset GSD II and extend life and improve quality of life in older people with late-onset GSD II. NBS provides the opportunity for early diagnosis of all cases of GSD II.

Why would the requestor seek to use the proposed investigative technology rather than the comparator(s)?

Compared to current practice of no universal screening, universal NBS for GSD II may provide significantly more health benefits than current practice, due to earlier diagnosis and treatment.

In the absence of NBS, targeted screening is offered to patients with a known family history, however it is limited, missing an unknown number of cases, and is far less comprehensive than universal screening. More cases will be identified earlier by NBS, and morbidity can be reduced by initiating earlier treatment. Burden on affected individuals will also be reduced by the avoidance of diagnostic delays and disease manifestations prior to treatment. Burdens on hospitals and the health system, patients and their caregivers may be reduced by lower levels of symptom severity and prevention of serious complications in early GSD II diagnosed individuals.

Identify how the proposed technology achieves the intended patient outcomes:

The proposed technology will offer earlier diagnosis and earlier initiation of treatment. Infantile-onset GSD II diagnosed from NBS enables earlier intervention which reduces mortality and morbidity. Late-onset GSD II diagnosis is beneficial through minimising the diagnostic odyssey / time taken to achieve diagnosis in cases where investigation only commences after the presentation of symptoms.

For some people, compared with the comparator(s), does the test information result in:
(please select your response for each statement)

A change in clinical management? ☒ Yes ☐ No

For patients with infantile-onset GSD II, life-saving treatment will be initiated earlier (see Identify how the proposed technology achieves the intended patient outcomes):

For patients with non-classic infantile-onset GSD II, and late-onset GSD II, diagnosis through NBS will result in earlier treatment initiation due to monitoring of clinical outcomes, and avoidance of the 'diagnostic odyssey' which may delay treatment initiation under the comparator.

A change in health outcome? ☒ Yes ☐ No

For patients with infantile-onset GSD II, earlier initiation of ERT, significantly alters the outcomes for babies. Without early treatment, symptom severity can mean early death, or use of ventilator.

For patients with late-onset GSD II, monitoring and subsequent early initiation of treatment can reduce symptom severity and improve quality of life.

Other benefits? ☒ Yes ☐ No

Please provide a rationale, and information on other benefits if relevant:
Cascade testing may results in additional benefits such as value of knowing, which can include information for reproductive planning, and life planning. Also avoiding the diagnostic odyssey can be a benefit to patients and their families.

In terms of the immediate costs of the proposed technology (and immediate cost consequences, such as procedural costs, testing costs etc.), is the proposed technology claimed to be more costly, the same cost or less costly than the comparator?

☒ More costly
☐ Same cost
☐ Less costly

Provide a brief rationale for the claim:
There is currently no universal screening (i.e., no cost). Introduction of universal screening will have associated costs and will therefore be more costly than no screening. However, due to screening en masse, the cost per assay should be greatly reduced. Targeted screening will still occur as it provides greater reproductive options for couples.

Newborns diagnosed with infantile-onset GSD II may receive ERT for longer with early diagnosis and initiation of treatment prior to symptom presentation. However, fewer symptomatic treatments are likely to be required, for example fewer respirators, and fewer hospitalisations may be needed, thus there will be some savings.

More individuals with late-onset GSD II may be diagnosed, who may previously have remained undiagnosed. These individuals may receive treatment where previously they did not. With reduced symptom severity following treatment, some individuals may be more productive, and lead more independent lives than before.

Introduction of NBS for GSD II is expected to be more costly than current screening and management but will likely result in cost savings across the lifespan of the individual with GSD II.

Summary of Evidence

Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology.

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
1.	Published research	Lessons Learned from Pompe Disease Newborn Screening and Follow-up (Klug et al 2020)	Early initiation of ERT led to normal development and cardiac improvement for most infantile onset Pompe disease cases, one patient has discontinued ERT due to infusion-related reactions. Of the 23 later-onset cases that were still in active follow-up, 20 patients were stable and did not require ERT.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7422965/	6 March 2020
2.	Published research	Respiratory function during enzyme replacement therapy in late-onset Pompe disease: longitudinal course, prognostic factors, and the impact of time from diagnosis to treatment start (Stockton et al, 2020)	FVC stability over 5 years suggests that respiratory function is preserved during long-term ERT in real-world settings. Early initiation of alglucosidase alfa was associated with preservation of FVC in LOPD patients with better respiratory function at the time of treatment initiation.clinically meaningful.	https://pubmed.ncbi.nlm.nih.gov/32524257/	October 2020
3.	Published research	Health and economic outcomes of newborn screening for infantile-onset Pompe disease (Richardson et al, 2021)	Infants with screened and treated infantile-onset Pompe disease experienced an average lifetime increase of 11.66 QALYs compared with clinical detection. The ICER was $379,000/QALY from a societal perspective and $408,000/QALY from the health-care perspective. Results were sensitive to the cost of enzyme replacement therapy. Conclusion: Newborn screening for Pompe disease results in substantial health gains for individuals with infantile-onset Pompe disease, but with additional costs.	https://pubmed.ncbi.nlm.nih.gov/33281187/	23 April 2021
4.	Published research	Clinical efficacy of the enzyme replacement therapy in patients with late-onset Pompe disease: a systematic review and a meta-analysis (Sarah et al, 2022)	A systematic review and meta-analysis published in 2022 concluded that ERT has a significant beneficial efficacy in the improvement of walking distance in LOPD patients and a non-significant improvement of muscle strength. No improvement in respiratory capacity was found in this study.	https://pubmed.ncbi.nlm.nih.gov/33851281/	Feb 2022

Algorithms

Preparation for using the health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, before patients would be eligible for the proposed health technology:
Not applicable as the proposed health technology does not have any associated eligibility criteria, all newborns are proposed to be screened.

Is there any expectation that the clinical management algorithm *before* the health technology is used will change due to the introduction of the proposed health technology?

☐ Yes
☒ No

Describe and explain any differences in the clinical management algorithm prior to the use of the proposed health technology vs. the comparator health technology:
Not applicable

Use of the health technology

Explain what other healthcare resources are used in conjunction with delivering the proposed health technology:
The test can be undertaken on the sample already collected through the NBS program; additional costs accrue and vary by the laboratory testing that is undertaken.

Explain what other healthcare resources are used in conjunction with the comparator health technology:
Confirmatory diagnostic testing that is currently undertaken when an individual presents with symptoms

Describe and explain any differences in the healthcare resources used in conjunction with the proposed health technology vs. the comparator health technology:
Additional costs associated with universal newborn screening before the confirmatory diagnostic testing that occurs in the absence of NBS (when patients present with symptoms).

Clinical management after the use of health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the proposed health technology:

Proposed clinical management of infantile-onset GSD II

Newborns who receive a positive NBS will receive confirmatory testing (urine Glc4 test or GAA sequencing). Those who are found to not have GSD II require no further intervention. Those who have a positive NBS (reduced or no enzyme activity) and have clinical evidence of cardiomyopathy (classic infantile-onset GSD II) will be treated with ERT as soon as CRIM status is determined. Those without evidence of cardiomyopathy (non-classic infantile-onset GSD II) will wait for confirmation before starting ERT. Infantile-onset GSD II is a progressive disease, so further treatments for symptom development will occur as required. Cascade testing will be offered to family members of newborns diagnosed with infantile-onset GSD II.

Proposed management of late-onset GSD II

Newborns who have a positive NBS (low to borderline enzyme activity) will receive confirmatory testing (urine Glc4 test or GAA sequencing). If confirmed positive for late-onset GSD II, the patients will be offered monitoringuntil the first signs or symptoms of disease show. ERT can be considered as soon as this occurs and without an extended diagnostic period. Cascade testing will be offered to family members of newborns diagnosed with late-onset GSD II.

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the comparator health technology:

Children and adults will be diagnosed once they present with symptoms. Once the symptoms suggest GSD II (which in adults can take some time) alpha glucosidase testing will be conducted on a blood sample. Confirmatory testing will be conducted by urine Glc4 assay or GAA sequencing. Once GSD II is confirmed ERT can be offered (see criteria for access to LSDP[3]).

Describe and explain any differences in the healthcare resources used *after* the proposed health technology vs. the comparator health technology:

The confirmatory tests (alpha glucosidase enzyme activity, urine Glc4 assay, *GAA* sequencing) used for the intervention are the same as the diagnostic tests used for the comparator.

However, more individuals will receive confirmatory testing with the proposed health technology than with the comparator health technology. This is due to the testing of newborns with false positive NBS results. With the comparator health technology, only children presenting with symptoms consistent with GSD II would be tested. According to the LSDP criteria, a child up to 24 months of age can access ERT prior to symptom onset. In current practice, patients won't get treated until after symptom onset and diagnosis[3].

Algorithms

Insert diagrams demonstrating the clinical management algorithm with and without the proposed health technology:

Current clinical management for infantile-onset GSD II

In the current management for infantile-onset GSD II, children <2 year of age are assessed once symptoms occur that are suggestive of GSD II. Once a clinical examination has been conducted, an alpha glucosidase activity assay is ordered on a blood sample (dried bloodspot sample in newborns). In those with low enzyme activity and cardiomyopathy (classic infantile-onset GSD II), CRIM status should be determined and ERT can be started in the patient. *GAA* sequencing will also be ordered for confirmation, but treatment should not wait for the results as the early implementation of ERT is critical to avoid worsening symptom development. In babies without cardiomyopathy and low alpha glucosidase activity, confirmation testing can be ordered by urine Glc4 assay or *GAA* sequencing. Once two tests are positive for GSD II, ERT should be started.

[3] LSDP eligibility criteria for Pompe disease: https://www.health.gov.au/sites/default/files/documents/2022/09/life-saving-drugs-program-pompe-disease-guidelines.pdf

Cascade testing and genetic counselling should be offered to relatives of those testing positive or who are found to be carriers.

The current management algorithm for infantile onset GSD II is in Figure 1.

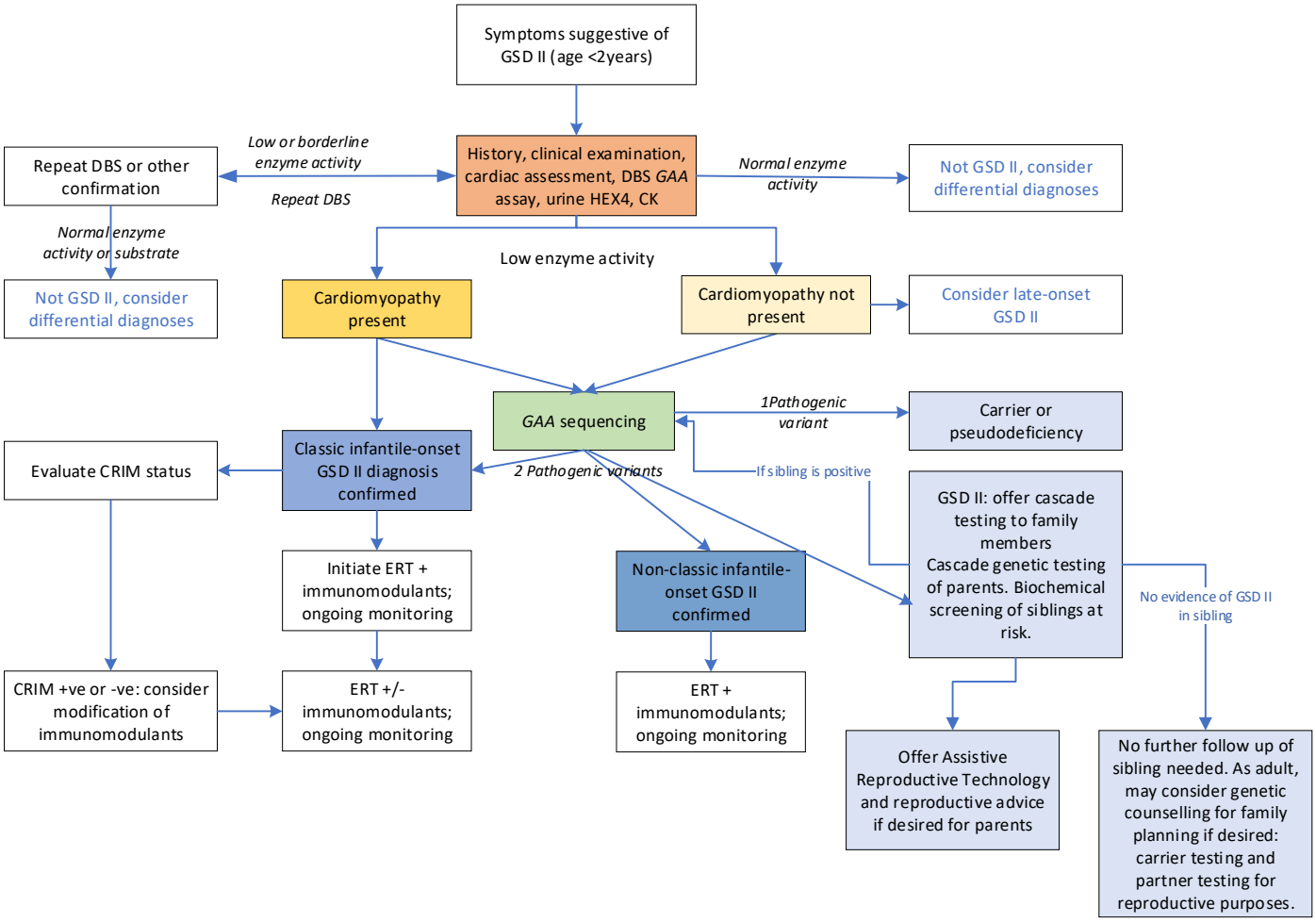


Figure 1 *Current clinical management algorithm for infantile-onset GSD II*

Abbreviations: CK = creatinine kinase assay; CRIM = cross-reactive immunological material; DBS = dried blood spot; ERT = enzyme replacement therapy; GAA = alpha glucosidase; GSD II = glycogen storage disease II; HEX4 = urine glucotetrasaccharides assay

Current management for late-onset GSD II

Late-onset GSD II can occur in children and adults over 1 to 2 years of age (there is overlap with those who are diagnosed with infantile-onset GSD II). The severity of symptoms and the rate of development is usually dependent on the level of enzyme activity in the individual. In adults, symptoms can develop slowly and may not be diagnosed for some time as they are often non-specific to GSD II. Once there are signs and symptoms suggestive of GSD II an alpha glucosidase assay should be ordered on patient blood. A positive test is usually repeated, and if still positive a confirmatory test can be ordered – usually *GAA* sequencing, but in some cases a tissue assay will be performed. If late-onset GSD II is confirmed, ERT can be started. Cascade testing and genetic counselling should be offered to relatives of those testing positive or who are found to be carriers.

The current management algorithm for late onset GSD II is in Figure 2.

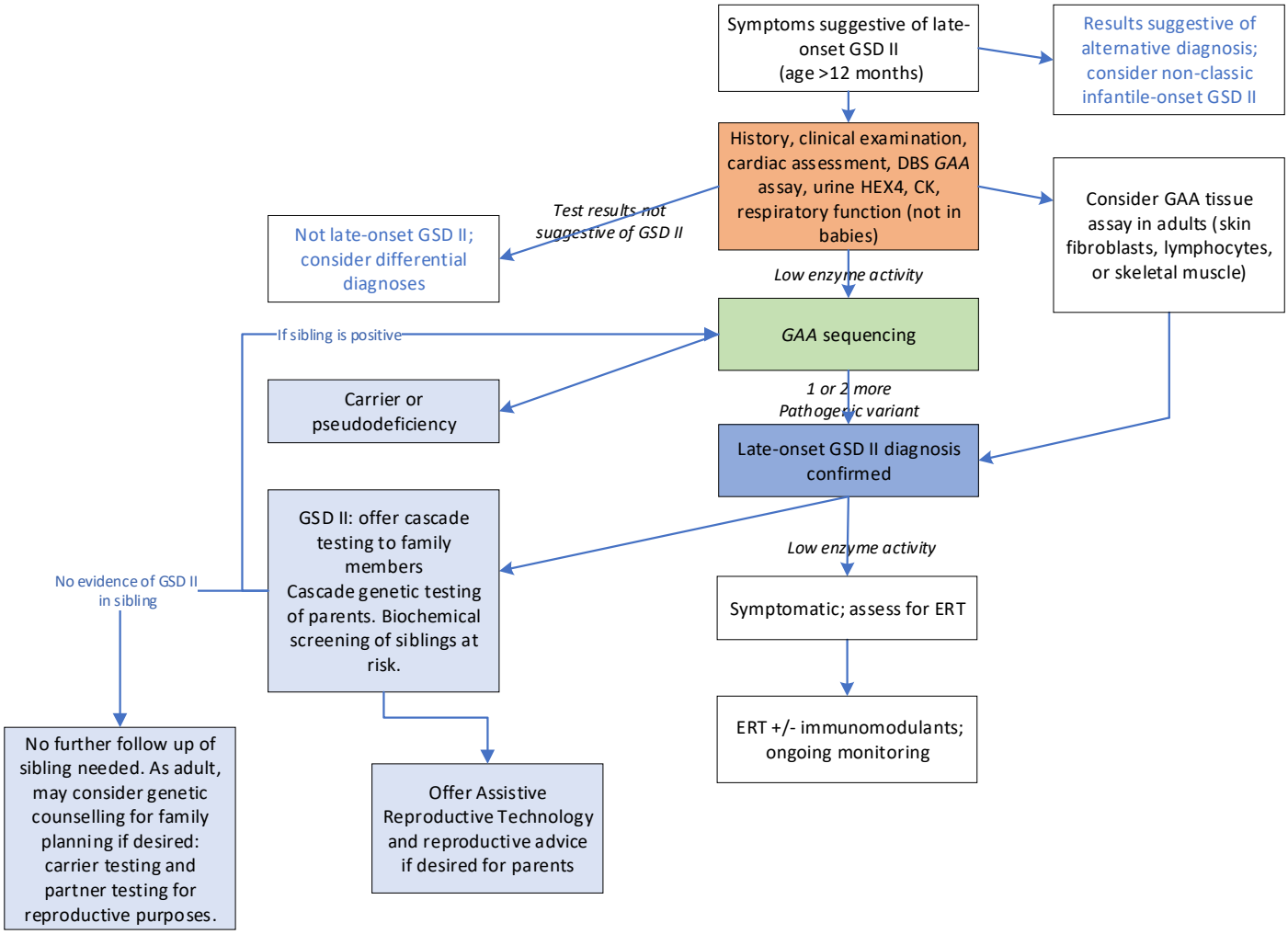


Figure 2 *Current clinical management algorithm for late-onset GSD II*

Abbreviations: CK = creatinine kinase assay; DBS = dried blood spot; ERT = enzyme replacement therapy; GAA = alpha glucosidase; GSD II = glycogen storage disease II; HEX4 = urine glucotetrasaccharides assay

Proposed management of infantile-onset and late-onset GSD II

Diagnosis of infantile-onset GSD II following NBS would occur in most cases prior to symptom development, although for those with infantile-onset GSD II, there is likely to be evidence of cardiomyopathy. ERT can be started as soon as signs of cardiomyopathy are detected in a newborn and CRIM status has be determined, or after confirmation of a positive enzyme activity screen, by GAA sequencing. Because testing is done in newborns, ERT can start earlier, and more severe outcomes can be avoided. Cascade testing and genetic counselling should be offered to relatives of those testing positive or who are found to be carriers.

In people with late-onset GSD II, diagnosis would occur in newborns, well before symptoms develop. After a positive screening results, a clinical assessment should show no signs of GSD II. GAA sequencing will be ordered. The presence of two pathogenic variants is diagnostic of GSD II. Patient diagnosed should be monitored regularly until symptom development. At first signs of disease, ERT should be considered for the reduction of severity. ERT is not usually offered until

first signs of symptoms. Cascade testing and genetic counselling should be offered to relatives of those testing positive or who are carriers.

The proposed management algorithm is in Figure 3.

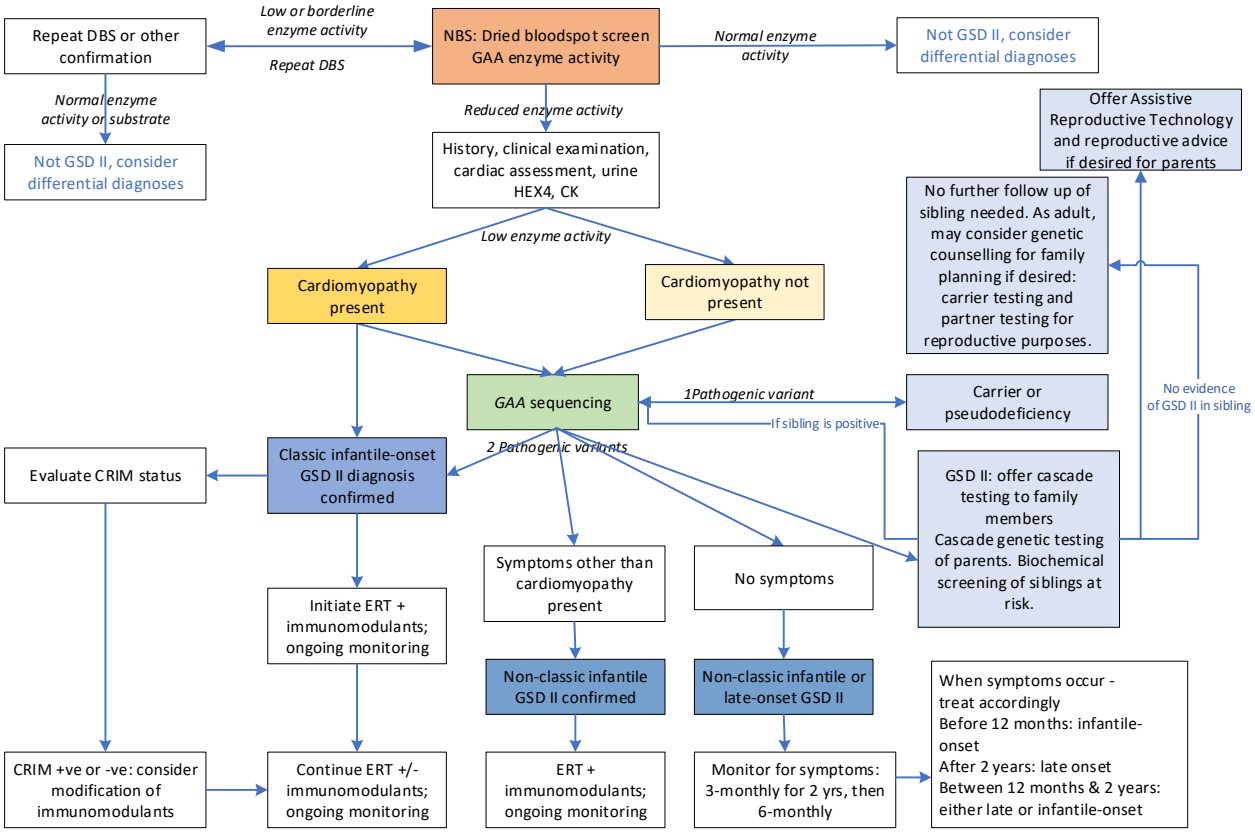


Figure 3 *Proposed clinical management algorithm for infantile-onset and late-onset GSD II*

Abbreviations: CK = creatinine kinase assay; CRIM = cross-reactive immunological material; DBS = dried blood spot; ERT = enzyme replacement therapy; GAA = alpha glucosidase; GSD II = glycogen storage disease II; HEX4 = urine glucotetrasaccharides assay